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(54) **Liquid suspension for oral administration.**

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(73) Proprietor: **ELAN CORPORATION P.L.C.**
Monksland Industrial Estate
Athlone County Westmeath(IE)

(72) Inventor: **Mulligan, Seamus**
4 Beech Lawn
Monksland Athlone County Westmeath(IE)

(74) Representative: **Goldin, Douglas Michael et al**
J.A. KEMP & CO. 14, South Square Gray's Inn
London WC1R 5EU (GB)

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Description

This invention relates to liquid antibiotic suspensions for oral administration. In particular, the invention relates to liquid antibiotic suspensions with improved bioavailability, release characteristics, inter-subject variability, and taste characteristics when compared with conventional liquid formulations.

Liquid formulations conventionally used in human or veterinary medicine are generally aqueous based suspensions or, alternatively, emulsions. Conventional aqueous based suspensions are sold as reconstitutable suspensions or ready-made suspensions, the latter type of suspensions being common in the U.S.A. However, with both types of suspensions there are strict storage requirements such as a requirement for refrigeration. Storage problems with such formulations result from their having a short shelf life. For example, antibiotics frequently fall within this category, in that they are aqueous based products with a short shelf life necessitating stringent storage conditions.

Non-aqueous carrier vehicles have not conventionally been used in liquid formulations for oral administration. There has been limited use of oils in such formulations but these have been as oil-in-water emulsions or water-in-oil emulsions.

US-A-3 996 355 describes stable suspensions of water sensitive drugs suitable for oral administration, in which the drug is suspended in an anhydrous vehicle comprising *inter alia* a vegetable oil. The anhydrous vehicle includes also a sugar suspending agent or if a sugar-free suspension is required the sugar agent is replaced by an effective amount of a silica thickening agent. Such suspensions are indicated to have bioavailabilities equal to those of the commercially available aqueous suspensions.

It is an object of the present invention to provide an oil based, liquid antibiotic suspension for oral administration having good shelf life and, in addition, having improved bioavailability, release characteristics, inter-subject variability and taste characteristics relative to conventional liquid formulations.

Accordingly, the invention provides a liquid antibiotic suspension for oral administration having improved bioavailability, comprising an antibiotic suspended in an edible, oily vehicle wherein the antibiotic is in the form of controlled release microparticles containing the antibiotic and optionally an excipient, the antibiotic of said microparticles being coated with, distributed through or absorbed onto at least one non-toxic polymer, and said microparticles further having an average size in the range 0.1 to 150 μm and a controlled release of antibiotic which in combination with the oily vehicle permits controlled absorption of antibiotic effective to improve the bioavailability of said antibiotic over that obtained in aqueous liquid suspensions.

Preferably the particles have an average size in the range 50 to 100 μm.

The oily vehicle is preferably an oil of animal, mineral or vegetable origin. Preferably, the oil is of mineral or vegetable origin. Preferred oils of vegetable origin are selected from: almond oil, arachis oil, castor oil, fractionated coconut oil, cotton seed oil, ethyl oleate oil, evening primrose oil, maize oil, olive oil, persic oil, poppy-seed oil, safflower oil, sesame oil, soya oil and sunflower oil. Especially preferred vegetable oils include fractionated coconut oil, soya oil or sunflower oil. In the case of fractionated coconut oil, the oil is suitably that sold under the Trade Mark MIGYLOL (Dynamit Nobel). An especially suitable oil for use as the oily vehicle is sucrose polyester as sold under the brand name Olestra.

In the case of mineral oils, suitable oils include silicone oil and paraffin or mineral oil.

Antibiotics for use as active ingredient in the liquid suspension according to the invention include all major classes of antibiotics, more particularly macrolides such as Erythromycin and Roxithromycin and penicillins such as Amoxycillin. Suitably the antibiotic is a macrolide or a salt thereof or a penicillin or salt or hydrate thereof. Preferably the antibiotic is selected from Erythromycin ethyl succinate, Roxithromycin, and Amoxicillin trihydrate.

It is found that the use of an oily vehicle as the carrier medium in suspension dosage forms according to the invention, either in capsule or liquid form, results in the performance of the active ingredient, in terms of its bioavailability, release characteristics, inter-subject variability, and taste characteristics being considerably improved over conventional liquid formulations.

The use of the oily vehicle will normally allow the product to exist as a ready-made suspension with an acceptable shelf life at normal and elevated temperatures without refrigeration. This advantage is extremely important when dealing with products that may have to be reconstituted where the water supply and storage facilities are poor.

The improvement in bioavailability in presence of controlled release characteristics may allow a lowering in the total daily dose and also the number of dosing intervals. This will be expected to result in a reduced incidence of side effects due to decreased total dose, and improved patient compliance, due to the increase in dosage interval.

The performance, both physiological and organoleptic, of the suspension according to the invention can be altered as necessary depending on the specific drug entity. Therefore, inclusion of sweetening agents such as sorbitol may be required to enhance the palatability of the product. Similarly, flavourings, preservatives, colourings and other pharmaceutical excipients may be included to enhance the organoleptic properties of the suspension. The suspension may also include an antioxidant such as, for example, butylated hydroxyanisole, butylated hydroxytoluene or propyl gallate or a mixture thereof.

The addition of certain other excipients may serve to change the in vivo performance of the product, for example, the inclusion of pharmaceutically acceptable surfactants to modify the drug absorption rate.

The antibiotic entity that is included in the suspension has been treated so as to affect its taste or release properties, for example, by microencapsulation or by various processes which modify such properties. Alternatively, the antibiotic entity may be in the form of an adsorbate, resinate or antibiotic complex. A process whereby a taste-masked formulation of the raw material can be produced is a process in accordance with our UK-A-2 166 651. A material so produced and sold under the Trade Mark PharmaZome may have controlled release characteristics or may taste-mask the drug material. More specifically, products sold under the Trade Mark PharmaZome comprise a controlled release powder containing discrete microparticles for use in edible, pharmaceutical and other controlled release compositions, said powder comprising particles containing an active ingredient and optionally an excipient in intimate admixture with at least one non-toxic polymer, each of said particles being in the form of a micromatrix with the active ingredient and excipient, if present, uniformly distributed throughout, said particles further have an average size in the range 0.1 to 125 μm and have a predetermined release of active ingredient.

More generally, PharmaZomes are spherical drug/polymer mixtures with a particle size of less than 125 μm, this particle size being below the threshold of mouth feel. When incorporated into the oily vehicle in the suspension according to the invention, they may reduce or eliminate the poor taste of some drug compounds.

In the accompanying drawings:

Fig. 1 is a graph of plasma concentration (μg/ml) versus time after administration (hours) for the formulation of Example 1 relative to a reference product;

Fig. 2 is a graph of plasma concentration (μg/ml) versus time after administration (hours) for the formulation of Example 3 relative to a reference product;

Fig. 3 is a graph of plasma concentration (μg/ml) versus time after administration (hours) for the formulation of Example 4 relative to a reference product; and

Fig. 4 is a graph of plasma concentration (μg/ml) versus time after administration (hours) for the formulation of Example 6 relative to a reference product.

The invention will be further illustrated by the following Examples.

EXAMPLE 1.

Sorbitol (20 kg), citric acid (5 g) and Tenox GT-1, an antioxidant, (20 g), were ball-milled with Soya Oil U.S.P. (76.7 kg) for twelve hours. The resulting dispersion of sorbitol in oil was transferred to a stirred vessel and the following added while stirring - Aerosil R972 colloidal silicon dioxide (Aerosil is a Trade Mark) (3.1 kg), creamy vanilla flavour (100 g), candy mint flavour (75 g).

Erythromycin ethyl succinate PharmaZomes as prepared in accordance with UK-A-2 166 651 were added to the above liquid vehicle to produce a suspension containing the equivalent of 250 mg/5 ml of erythromycin as base. The formulation thereby produced was a ready-made suspension of Erythromycin ethyl succinate.

EXAMPLE 2.

Example 1 was repeated except the oil used was sunflower oil.

EXAMPLE 3.

Sucrose (1 kg) and Tenox GT-1, an antioxidant, (1 g) were ball-milled with Soya Oil U.S.P. (8 kg). To the resulting dispersion was added the following -

Aerosil (Trade Mark)	0.4 kg
Butterscotch flavour	0.01 kg
Vanilla flavour	0.005 kg
Drewpol 3-1-0	0.2 kg
Drewpol 10-4-0	0.2 kg

Drewpol is a Trade Mark of PVO International Inc. and is used to denote various grades of polyglyceryl partial esters of edible fats and/or oils or their fatty acids up to and including the decaglyceryl esters.

The mixture was well mixed to obtain an even dispersion. Amoxycillin trihydrate PharmaZomes as prepared in accordance with UK-A-2 166 651 were added to the above vehicle to obtain a suspension comprising 250 mg Amoxycillin as base per 5 ml.

EXAMPLE 4.

Example 5 was repeated except taste-masked Amoxycillin coated with Ethocel (ethyl cellulose) in a fluid bed was included as the active ingredient to give a 250 mg Amoxycillin as base per 5 ml.

EXAMPLE 5.

Example 1 was repeated except Erythromycin ethyl succinate coated with ethylcellulose was submitted in microcapsule form prepared by a coascervation method necessary adjustments were made to give a 250 mg Erythromycin as base per 5 ml suspension.

EXAMPLE 6.

Roxithromycin (a macrolide) PharmZomes were prepared according to UK-A-2 166 651 with a potency of 712 mg/g. These Roxithromycin PharmaZomes were then incorporated into a pleasantly flavoured suspension vehicle to achieve a potency of 100 mg/5 ml, and provided for a pleasant tasting, ready-made suspension, exhibiting improved bioavailability, release and inter-subject variability. The final suspension consisted of:

Cottonseed oil U.S.P.	96.34%
Roxithromycin PharmaZomes	2.81%
Tenox GT-1 (Trade Mark)	0.05%
Aerosil R972 (Trade Mark)	0.5%
Cherry flavour	0.1%
Aspartame	0.2%

PHARMACOLOGICAL DATA.

1. The formation of Example 1 was tested in six subjects in a two-way crossover single-dose comparison study with a reference product comprising a conventional reconstitutable suspension having an aqueous base of Erythromycin ethyl succinate and hereinafter referred to as "reference".

The reference was administered as 400 mg at 0 hours while the formulation of Example 1 was administered as 400 mg also at 0 hours. Plasma was sampled out to 12 hours and the mean results calculated and tabulated. The results are shown in Table 1 and accompanying Fig. 1. A range of pharmacokinetic parameters are given in Table 2 and time-cover in Table 3.

TABLE 1.

Mean serum concentrations of Erythromycin (as ethyl succinate) comparing the formulation of Example 1 with reference.

No. of subjects: N = 6 (young healthy male subjects). Plasma levels are in μg/ml.

TIME (Hours)	REFERENCE	EXAMPLE 1
0.00	0.00	0.00
0.50	1.09	0.17

TABLE 1./contd.

TIME (Hours)	REFERENCE	EXAMPLE 1
1.00	1.01	0.68
2.00	0.56	1.35
3.00	0.39	0.83
4.00	0.32	0.84
5.00	0.20	0.69
6.00	0.09	0.61
8.00	0.00	0.49
12.00	0.00	0.18

TABLE 2

Pharmacokinetic Parameters		
PHARMACOKINETIC PARAMETER	REFERENCE	EXAMPLE 1
AUC (0 - 12 h)	2.96	7.06
AUC (0 - ∞)	3.33	7.53
F∞ (%)	100.00	225.30
Cmax	1.22	1.51
tmax	0.58	2.67
t 1/2	1.99	5.98
Cmax/C(t)	10.70	2.44

TABLE 3

Time-Cover (Hours)		
CONCENTRATIONS (μg/ml)	REFERENCE	EXAMPLE 1
0.25	4.15	9.11
0.50	2.17	5.57
0.75	1.04	3.07
1.00	0.48	1.59

DISCUSSION.

From the above Tables and accompanying Fig. 1 it will be observed that the formulation of Example 1 shows remarkably increased bioavailability (F∞ = 225.30) compared to reference (= 100), as further witnessed by AUC (∞) values of 7.53 for the formulation of Example 1 compared to 3.33 for reference. This was further coupled with a clear demonstration of improved absorption as evidenced by the increased tmax (2.67 h) for the formulation of Example 1, compared to reference (= 0.58). The formulation also exhibits markedly extended time-cover at all concentration levels, but most noticeably for those up to 1.00 μg/ml, with the formulation of Example 1 giving 1.59 hours of cover at 1.00 μg/ml as against 0.48 hours for reference, over 3 times the time cover. The half-life (t 1/2) is also greatly increased for the formulation of Example 1 (5.98) compared to reference (1.99).

As both the formulation of Example 1 and reference have the same pharmaceutically active ingredient (Erythromycin ethyl succinate) and are administered in the same total dose over 12 hours, the following characteristics of:

* Greatly increased bioavailability
* Improved absorption
* Greatly increased time-cover at a range of plasma levels
* Markedly increased half-life

result from the use of an oily vehicle as the carrier medium.

2. The formulation of Example 3 was tested in six subjects in a two-way crossover single-dose comparison study with a reference product comprising a conventional reconstitutable suspension having an aqueous base of Amoxicillin and hereinafter referred to as "reference".

Both the reference and formulation of Example 3 were administered as a single dose of 250 mg at 0 hours. Plasma was sampled out to 12 hours and the mean results calculated and tabulated. The results are shown in Table 4 and accompanying Fig. 2. A range of pharmacokinetic parameters are given in Table 5.

TABLE 4

Mean serum concentrations of Amoxicillin comparing the formulation of Example 3 with reference.

No. of subjects: N = 6 (young healthy male subjects). Plasma levels are in µg/ml.

TIME (Hours)	REFERENCE	EXAMPLE 3
0.00	0.00	0.00
0.25	2.41	0.58
0.50	4.25	2.29
0.75	5.69	3.63
1.00	4.44	3.67
1.50	3.37	3.95
2.00	2.91	3.52
3.00	1.18	2.40
4.00	0.66	1.40
6.00	0.18	0.36
8.00	0.06	0.07
12.00	0.00	0.00

TABLE 5

Pharmacokinetic Parameters		
PHARMACOKINETIC PARAMETER	REFERENCE	EXAMPLE 5
AUC (0 - 12 h)	11.34	13.03
AUC (0 - ∞)	11.32	13.00
F∞ (%)	100.0	115.51
tmax	0.71	1.25
Cmax	5.99	4.80

DISCUSSION.

The formulation of Example 3 exhibits increased bioavailability (F∞ = 115.51) compared to reference (= 100). A significant extension of the tmax is also observed, with 0.71 hours and 1.25 hours for reference and formulation of Example 3 respectively, thus exhibiting the improved absorption tendencies of the formulation in the oily vehicle. As both the reference and formulation of Example 3 contain the same pharmaceutically active ingredient and are administered at the same dose, it is apparent that the

characteristics of:

* Increased bioavailability
* Improved absorption

result from the use of an oily vehicle as the suspension medium for the formulation of Example 3.

4. The formulation of Example 4 was tested in five subjects in a two-way crossover single dose comparison study with a reference product comprising a conventional reconstitutable suspension having an aqueous base of Amoxicillin and hereinafter referred to as "reference".

Both the formulation of Example 4 and the reference were administered as a 125 mg dose of Amoxicillin at 0 hours. Plasma was sampled out to 8 hours and the mean results calculated and tabulated. The results are shown in Table 6 and accompanying Fig. 3. A range of pharmacokinetic parameters are given in Table 7 and time-cover in Table 8.

TABLE 6

Mean serum concentrations of Amoxicillin comparing the formulation of Example 4 with reference.

No. of subjects: N = 5 (young healthy male subjects). Plasma levels are in µg/ml.

TIME (hours)	REFERENCE	EXAMPLE 4
0.00	0.00	0.00
0.25	1.84	0.46
0.50	4.28	1.88
0.75	4.22	3.51
1.00	3.44	3.82
1.50	2.28	3.81
2.00	1.41	2.72

TABLE 6 ./Contd.

TIME (hours)	REFERENCE	EXAMPLE 4
2.50	-	1.88
3.00	0.65	1.29
4.00	0.31	0.69
6.00	0.10	0.18
8.00	0.04	0.03

TABLE 7

Pharmacokinetic Parameters		
PHARMACOKINETIC PARAMETER	REFERENCE	EXAMPLE 4
AUC (0 - 8 h)	7.42	9.50
F (t) %	100.00	128.03
AUC (0 - ∞)	7.50	9.58
F∞ (t) %	100.00	127.19
Cmax	4.61	4.29
tmax	0.60	1.10

TABLE 8

Time-Cover (Hours)		
CONCENTRATIONS (µg/ml)	REFERENCE	EXAMPLE 4
1.00	2.42	3.09
2.00	1.38	1.90
3.00	0.79	1.05
4.00	0.29	0.37

DISCUSSION.

The formulation as prepared in Example 4, exhibits an all round improvement in relation to in vivo performance. When compared with the reference, in a panel of five young healthy male subjects, a significant increase in overall bioavailability is acheived (F∞ = 127.19) over reference (= 100). This increased bioavailability is not, however, achieved to the detriment of the complete profile of the formulation of Example 4, but rather compliments the improved absorption characteristics obtained as witnessed by the tmax extension from 0.6 h with reference to 1.10 h with formulation of Example 4. A characteristic flattening of the overall curve is observed, with a concomitant depression in the Cmax. This profile points to the further advantages of reduced peak: trough ratio (Cmax/Cmin) which would be even more evident at steady-state. The slight depression in Cmax obtained with the formulation of Example 4, and the plateau-like curve-peak observed as a result, serve to increase the length of time over which various plasma levels of Amoxicillin are obtained, as evidenced by Time-cover, whereby increases are seen with the formulation of

Example 4, in the amount of time in which plasma levels of 1.00, 2.00, 3.00 and 4.00 µg/ml are obtained.

Therefore, the formulation of Example 4 exhibits:

* Increased bioavailability over reference.
* Improved absorption characteristics.
* Decreased peak-to-trough fluctuations.

As the active ingredient is identical in chemical form and dose for both reference and the formulation of Example 4 it is obvious that the oily carrier vehicle is central in producing the observed improvements in performance. The formulation of Example 4 was also a pleasant tasting ready-made suspension.

5. The formulation of Example 6 was tested in three subjects in a two-way crossover single-dose comparison study with a reference product comprising Roxithromycin PharmaZomes in aqueous medium (i.e., an aqueous suspension) as a reconstitutable suspension and hereinafter referred to as "reference".

The reference was administered as 150 mg at 0 hours while the formulation of Example 6 was administered as 150 mg also at 0 hours. Plasma was sampled out to 24 hours and the mean results calculated and tabulated. The results are shown in Table 9 and accompanying Fig. 4. A range of pharmacokinetic parameters are given in Table 10 and time-cover in Table 11.

TABLE 9.

Mean serum concentrations of Roxithromycin comparing the formulation of Example 6 with reference.

No. of subjects: N = 3 (young healthy male subjects).
Plasma levels are in µg/ml.

TIME (Hours)	REFERENCE	EXAMPLE 6
0.00	0.00	0.00
0.50	0.68	0.46

TABLE 9 ./contd.

TIME (Hours)	REFERENCE	EXAMPLE 6
1.00	1.34	2.39
1.50	1.76	3.09
2.00	2.45	3.63
3.00	3.79	4.33
4.00	3.12	4.77
6.00	2.49	3.22
8.00	1.95	2.56
12.00	1.33	1.81
16.00	0.87	1.46
24.00	0.62	1.06

TABLE 10

Pharmacokinetic Parameters		
PHARMACOKINETIC PARAMETER	REFERENCE	EXAMPLE 6
AUC (0 - 24 h)	36.06	51.54
AUC (0 - ∞)	43.86	75.66
F∞ (%)	100.00	195.17
Cmax	3.79	5.01
tmax	3.00	3.17
t 1/2	8.88	16.21
Cmax/C(t)	6.12	4.66
Kel	0.08	0.043

TABLE 11

Time-Cover (Hours)		
CONCENTRATIONS (μg/ml)	REFERENCE	EXAMPLE 6
1.00	15.03	20.51
2.00	5.75	9.88
3.00	1.89	5.05
4.00	1.13	1.93

DISCUSSION.

From the above Tables and accompanying Fig. 4 it will be observed that the formulation of Example 6 shows remarkably increased bioavailability ($F\infty$ = 195,17) compared to reference (= 100), as further witnessed by AUC (∞) values of 75.66 for the formulation of Example 6 compared to 43.86 for reference. It is also clear from Fig. 4 that the formulation of Example 6 exhibits controlled absorption. Even after 24 hours post administration the formulation of Example 6 achieves plasma concentrations approximately twice those of reference. The formulation also exhibits markedly extended time-cover at all concentration levels. The half-life (t 1/2) is also greatly increased for the formulation of Example 6 (16.21) compared to reference (8.88).

As both the formulation of Example 6 and reference have the same pharmaceutically active ingredient (Roxithromycin) and are formulated similarly in accordance with UK-A-2 166 651 and are administered in the same total dose over 24 hours, the following characteristics of:

* Greatly increased bioavailability
* Improved absorption
* Greatly increased time-cover at a range of plasma levels
* Markedly increased half-life

result from the use of an oily vehicle as the carrier medium. The formulation of Example 6 is also a pleasant tasting ready-made suspension.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A liquid antibiotic suspension for oral administration having improved bioavailability, comprising an antibiotic suspended in an edible, oily vehicle wherein the antibiotic is in the form of controlled release microparticles containing the antibiotic and optionally an excipient, the antibiotic of said microparticles being coated with, distributed through or absorbed onto at least one non-toxic polymer, and said microparticles further having an average size in the range 0.1 to 150 µm and a controlled release of antibiotic which in combination with the oily vehicle permits controlled absorption of antibiotic effective to improve the bioavailability of said antibiotic over that obtained in aqueous liquid suspensions.

2. A liquid suspension according to Claim 1, characterised in that the oily vehicle is an oil of animal, mineral or vegetable origin.

3. A liquid suspension according to Claim 2, characterised in that the oil is an oil of vegetable origin selected from almond oil, arachis oil, castor oil, fractioned coconut oil, cotton seed oil, ethyl oleate oil, evening primrose oil, maize oil, olive oil, persic oil, poppy-seed oil, safflower oil, sesame oil, soya oil, sunflower oil and sucrose polyester.

4. A liquid suspension according to Claim 2, characterised in that the oil is paraffin oil or silicone oil.

5. A liquid suspension according to any preceding claim, characterised in that the antibiotic is a macrolide or a salt thereof or a penicillin or salt or hydrate thereof.

6. A liquid suspension according to Claim 5, characterised in that the antibiotic is selected from Erythromycin ethyl succinate, Roxithromycin, and Amoxicillin trihydrate.

7. A liquid suspension according to any preceding claim, characterised in that it is in the form of capsules.

Claims for the following Contracting States : ES, GR

1. A process for preparing a liquid antibiotic suspension for oral administration having improved bioavailability, which comprises suspending an antibiotic in the form, of controlled release microparticles containing the antibiotic and optionally an excipient in an edible, oily vehicle, the antibiotic of said microparticles being coated with, distributed through or absorbed onto at least one non-toxic polymer, and said microparticles further having an average size in the range 0.1 to 150 µm and a controlled release of antibiotic which in combination with the oily vehicle permits controlled absorption of antibiotic effective to improve the bioavailability of said antibiotic over that obtained in aqueous liquid suspen-

sions.

2. A process according to Claim 1, characterised in that the oily vehicle is an oil of animal, mineral or vegetable origin.

3. A process according to Claim 2, characterised in that the oil is an oil of vegetable origin selected from almond oil, arachis oil, castor oil, fractioned coconut oil, cotton seed oil, ethyl oleate oil, evening primrose oil, maize oil, olive oil, persic oil, poppy-seed oil, safflower oil, sesame oil, soya oil, sunflower oil and sucrose polyester.

4. A process according to Claim 2, characterised in that the oil is paraffin oil or silicone oil.

5. A process according to any preceding claim, characterised in that the antibiotic is a macrolide or a salt thereof or a penicillin or salt or hydrate thereof.

6. A process according to Claim 5, characterised in that the antibiotic is selected from Erythromycin ethyl succinate, Roxithromycin, and Amoxicillin trihydrate.

7. A process according to any preceding claim, characterised in that it is in the form of capsules.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Flüssige antibiotische Suspension zur oralen Verabreichung mit verbesserter Bioverfügbarkeit, umfassend ein Antibiotikum suspendiert in einem eßbaren, öligen Vehikel, worin das Antibiotikum in Form von Mikropartikeln mit kontrollierter Freigabe vorliegt, die das Antibiotikum und gegebenenfalls einen Exzipienten enthalten, wobei das Antibiotikum der Mikropartikel beschichtet ist mit, verteilt ist über oder absorbiert ist auf mindestens einem nicht-toxischen Polymer, und die Mikropartikel weiter eine durchschnittliche Größe in dem Bereich von 0,1 bis 150 µm haben, und eine kontrollierte Freigabe des Antibiotikums, das in Kombination mit dem öligen Vehikel kontrollierte Absorption des Antibiotikums erlaubt, wirksam, um die Bioverfügbarkeit das Antibiotikums gegenüber jener in wässrigen flüssigen Suspensionen erreichten zu verbessern.

2. Flüssige Suspension nach Anspruch 1, dadurch gekennzeichnet, daß das ölige Vehikel ein Öl von tierischer, mineralischer oder pflanzlicher Herkunft ist.

3. Flüssige Suspension nach Anspruch 2, dadurch gekennzeichnet, daß das Öl pflanzlicher Herkunft ist, ausgewählt aus Mandelöl, Erdnußöl, Rizinusöl, fraktioniertem Kokosnußöl, Baumwollsaatöl, Ethyloleatöl, Nachtkerze (evening primrose oil), Maisöl, Olivenöl, Pfirsichkernöl, Mohnsamenöl, Carthamusöl, Sesamöl, Sojaöl, Sonnenblumenöl und Sucrosepolyester.

4. Flüssige Suspension nach Anspruch 2, dadurch gekennzeichnet, daß das Öl Paraffinöl oder Siliconöl ist.

5. Flüssige Suspension nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß das Antibiotikum ein Macrolid oder ein Salz davon oder ein Penicillin oder ein Salz oder Hydrat davon ist.

6. Flüssige Suspension nach Anspruch 5, dadurch gekennzeichnet, daß das Antibiotikum ausgewählt ist aus Erythromycinethylsuccinat, Roxithromycin und Amoxicillintrihydrat.

7. Flüssige Suspension nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß sie in Form von Kapseln vorliegt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer flüssigen antibiotischen Suspension zur oralen Verabreichung mit verbesserter Bioverfügbarkeit, welches umfaßt Suspendieren eines Antibiotikums in Form von Mikropartikeln mit kontrollierter Freigabe, die das Antibiotikum und gegebenenfalls einen Exzipienten in einem

eßbaren, öligen Vehikel enthalten, wobei das Antibiotikum der Mikropartikel beschichtet ist mit, verteilt ist über oder absorbiert ist auf mindestens einem nicht-toxischen Polymer, und die Mikropartikel weiter eine durchschnittliche Größe in dem Bereich von 0,1 bis 150 µm haben, und eine kontrollierte Freigabe des Antibiotikums, das in Kombination mit dem öligen Vehikel kontrollierte Absorption des Antibiotikums erlaubt, wirksam, um die Bioverfügbarkeit das Antibiotikums gegenüber jener in wässrigen flüssigen Suspensionen erreichten zu verbessern.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das ölige Vehikel ein Öl von tierischer, mineralischer oder pflanzlicher Herkunft ist.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Öl pflanzlicher Herkunft ist, ausgewählt aus Mandelöl, Erdnußöl, Rizinusöl, fraktioniertem Kokosnußöl, Baumwollsaatöl, Ethyloleatöl, Nachtkerze (evening primrose oil), Maisöl, Olivenöl, Pfirsichkernöl, Mohnsamenöl, Carthamusöl, Sesamöl, Sojaöl, Sonnenblumenöl und Sucrosepolyester.

4. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Öl Paraffinöl oder Siliconöl ist.

5. Verfahren nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß das Antibiotikum ein Macrolid oder ein Salz davon oder ein Penicillin oder ein Salz oder Hydrat davon ist.

6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das Antibiotikum ausgewählt ist aus Erythromycinethylsuccinat, Roxithromycin und Amoxicillintrihydrat.

7. Verfahren nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß sie in Form von ,Kapseln vorliegt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Suspension liquide d'antibiotique, destinée à l'administration par voie orale, ayant une biodisponibilité améliorée, comprenant un antibiotique en suspension dans un véhicule huileux comestible, dans laquelle l'antibiotique est sous la forme de microparticules à libération contrôlée contenant l'antibiotique et éventuellement un excipient, l'antibiotique desdites microparticules étant enrobé avec, réparti dans, ou absorbé par au moins un polymère non toxique, et lesdites microparticules ayant en outre une taille moyenne dans la gamme de 0,1 à 150 µm, et une libération contrôlée d'antibiotique qui, en combinaison avec le véhicule huileux, permet une absorption contrôlée de l'antibiotique, agissant de façon à améliorer la biodisponibilité dudit antibiotique par rapport à celle obtenue dans des suspensions liquides aqueuses.

2. Suspension liquide selon la revendication 1, caractérisée en ce que le véhicule huileux est une huile d'origine animale, minérale ou végétale.

3. Suspension liquide selon la revendication 2, caractérisée en ce que l'huile est une huile d'origine végétale, choisie parmi l'huile d'amande, l'huile d'arachide, l'huile de ricin, l'huile de coco raffinée, l'huile de graines de coton, l'huile d'oléate d'éthyle, l'huile de primevère, l'huile de maïs, l'huile d'olive, l'huile persique, l'huile de graines de pavot, l'huile de carthame, l'huile de sésame, l'huile de soja, l'huile de tournesol et le polyester de sucrose.

4. Suspension liquide selon la revendication 2, caractérisée en ce que l'huile est de l'huile de paraffine ou de l'huile de silicone.

5. Suspension liquide selon l'une quelconque des revendications précédentes, caractérisée en ce que l'antibiotique est un macrolide ou un de ses sels ou une penicilline ou un de ses sels ou hydrates.

6. Suspension liquide selon la revendication 5, caractérisée en ce que l'antibiotique est choisi parmi l'éthylsuccinate d'Erythromycine, la Roxithromycine et l'Amoxicilline trihydratée.

7. Suspension liquide selon l'une quelconque des revendications précédentes, caractérisée en ce qu'elle se trouve sous la forme de capsules.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'une suspension liquide d'antibiotique, destinée à l'administration par voie orale, ayant une biodisponibilité améliorée, consistant à mettre un antibiotique en suspension dans un véhicule huileux comestible, sous la forme de microparticules à libération contrôlée contenant l'antibiotique et éventuellement un excipient, l'antibiotique desdites microparticules étant enrobé avec, réparti dans, ou absorbé par au moins un polymère non toxique, et lesdites microparticules ayant en outre une taille moyenne dans la gamme de 0,1 à 150 µm, et une libération contrôlée d'antibiotique qui, en combinaison avec le véhicule huileux, permet une absorption contrôlée de l'antibiotique, agissant de façon à améliorer la biodisponibilité dudit antibiotique par rapport à celle obtenue dans des suspensions liquides aqueuses.

2. Procédé selon la revendication 1, caractérisé en ce que le véhicule huileux est une huile d'origine animale, minérale ou végétale.

3. Procédé selon la revendication 2, caractérisé en ce que l'huile est une huile d'origine végétale, choisie parmi l'huile d'amande, l'huile d'arachide, l'huile de ricin, l'huile de coco raffinée, l'huile de graines de coton, l'huile d'oléate d'éthyle, l'huile de primevère, l'huile de maïs, l'huile d'olive, l'huile persique, l'huile de graines de pavot, l'huile de carthame, l'huile de sésame, l'huile de soja, l'huile de tournesol et le polyester de sucrose.

4. Procédé selon la revendication 2, caractérisé en ce que l'huile est de l'huile de paraffine ou de l'huile de silicone.

5. Procédé selon l'une quelconque des revendications précédentes, caractérisé en ce que l'antibiotique est un macrolide ou un de ses sels ou une penicilline ou un de ses sels ou hydrates.

6. Procédé selon la revendication 5, caractérisé en ce que l'antibiotique est choisi parmi l'éthylsuccinate d'Erythromycine, la Roxithromycine et l'Amoxicilline trihydratée.

7. Procédé selon l'une quelconque des revendications précédentes, caractérisé en ce que la suspension se trouve sous la forme de capsules.

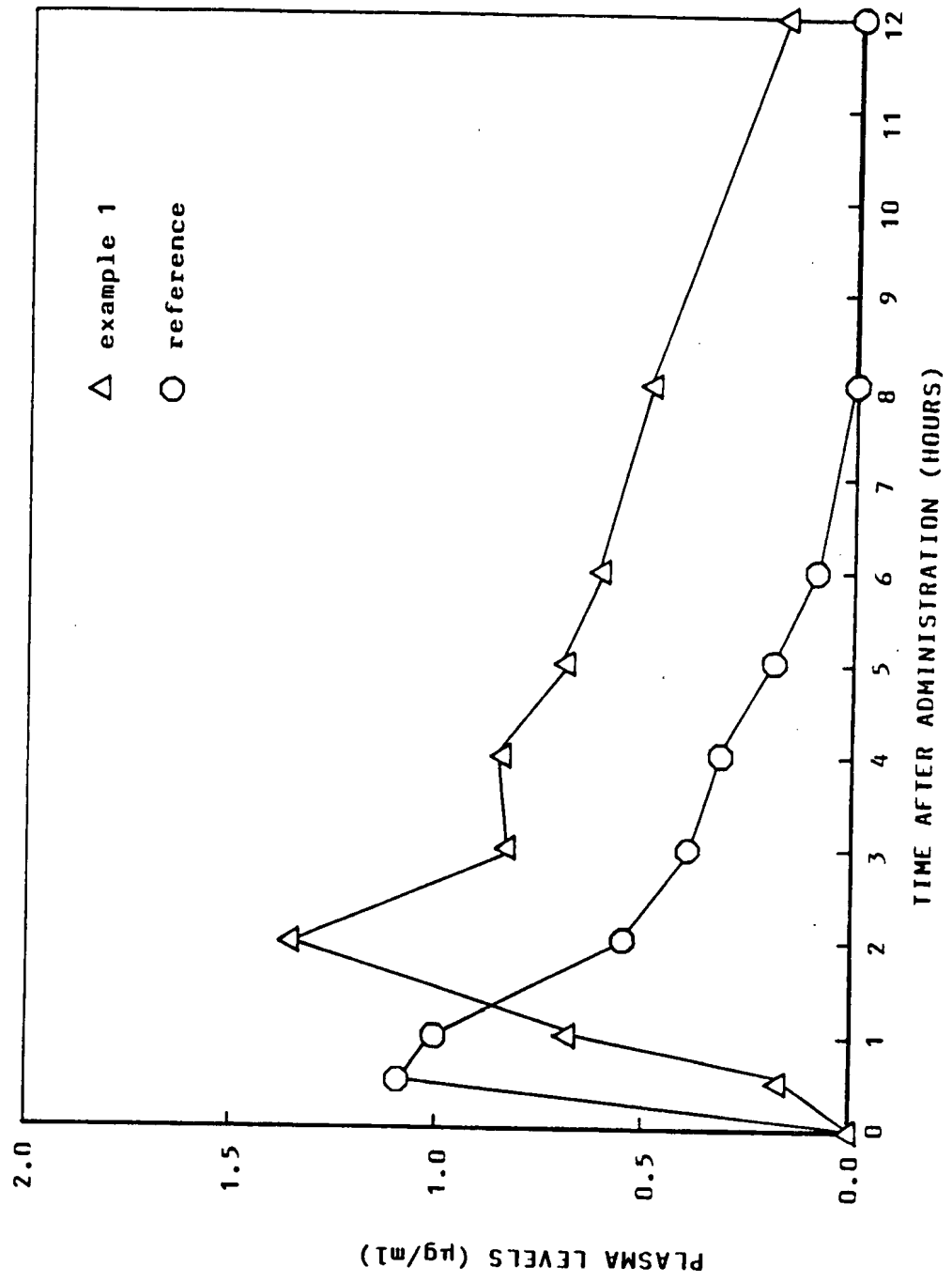
example 1
reference
PLASMA LEVELS (µg/ml)
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
8
9
10
11
12
TIME AFTER ADMINISTRATION (HOURS)

FIG.1

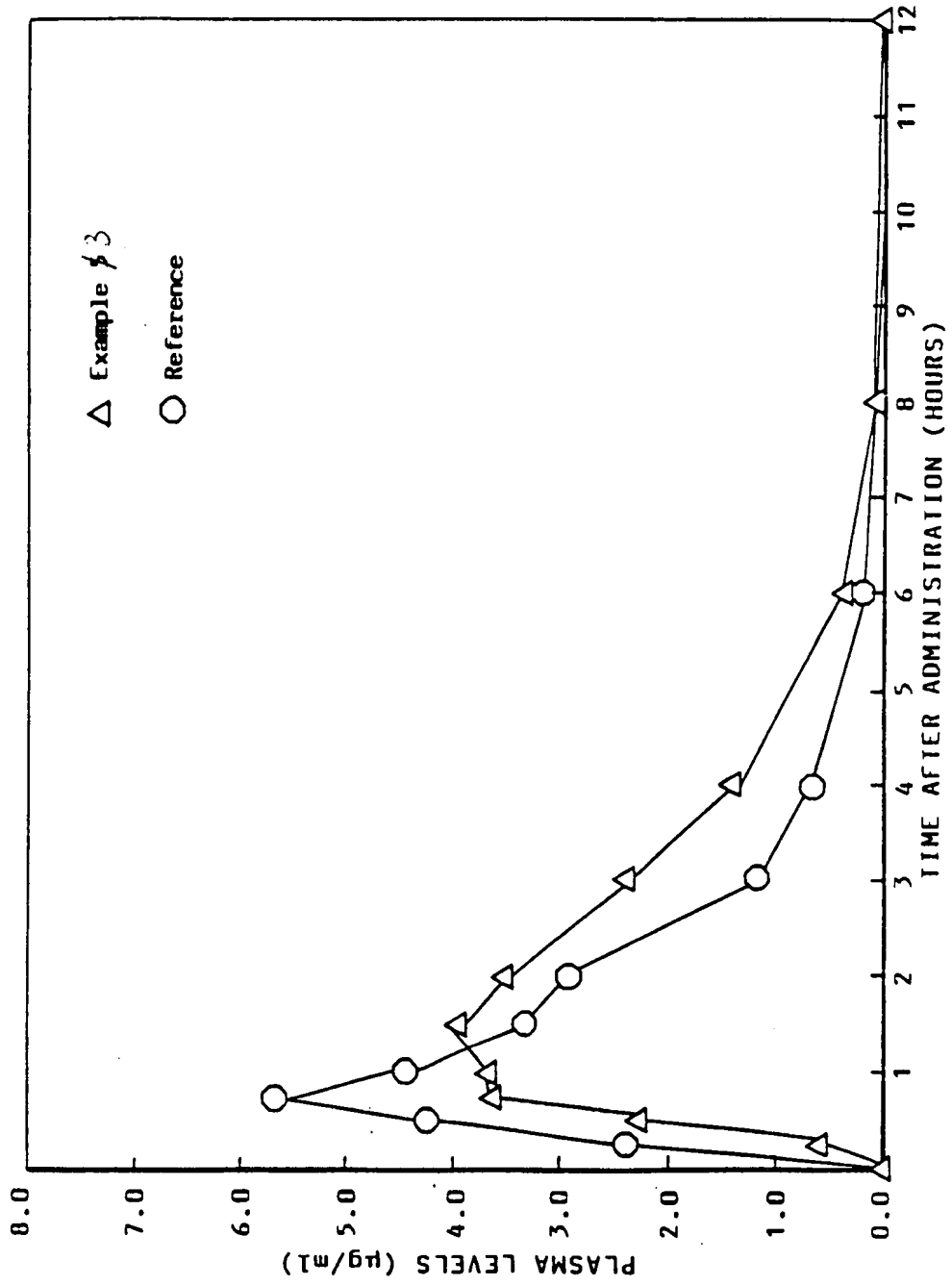
△ Example 3
○ Reference
PLASMA LEVELS (μg/ml)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1
2
3
4
5
6
7
8
9
10
11
12
TIME AFTER ADMINISTRATION (HOURS)

FIG 2

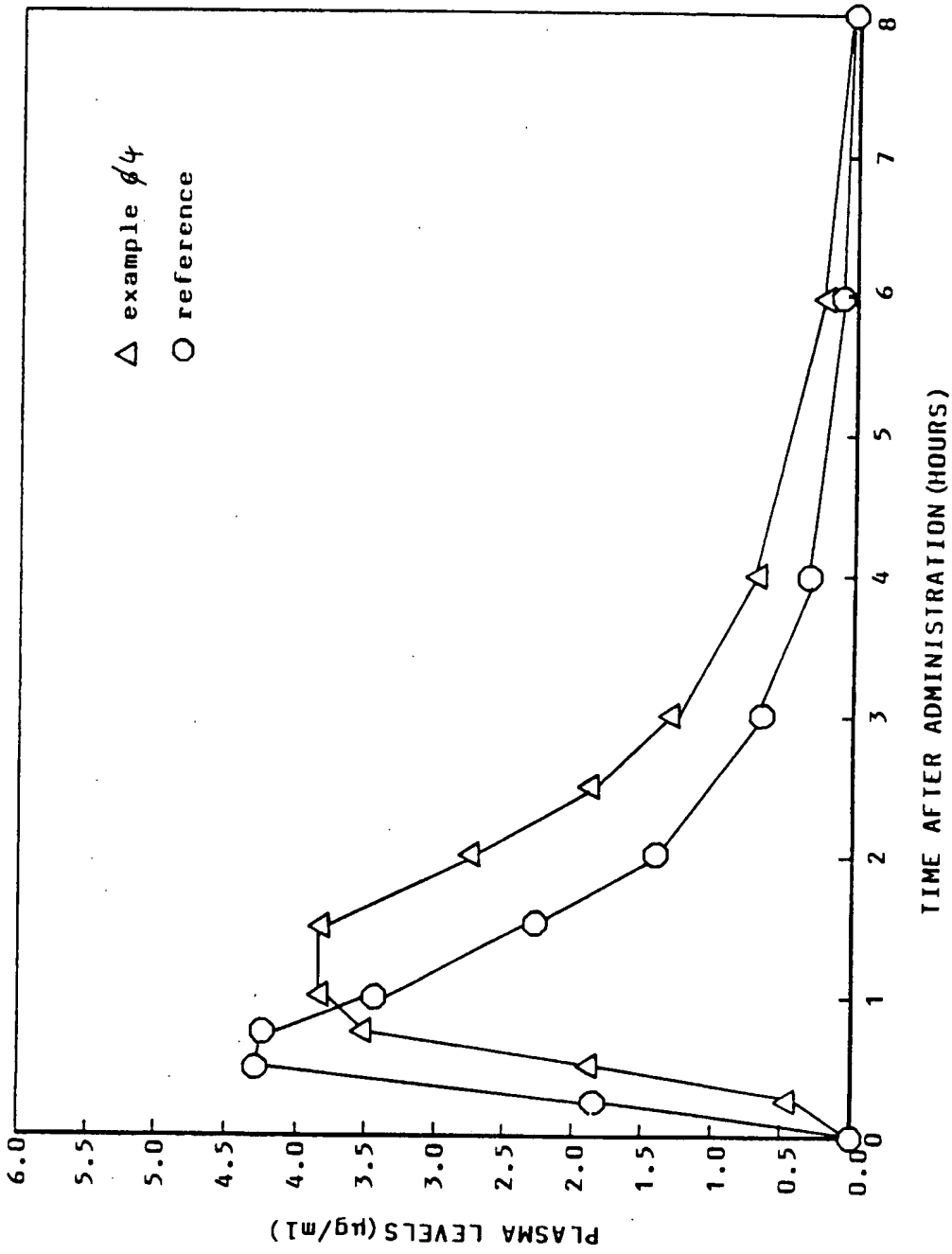
△ example #4
○ reference
PLASMA LEVELS (μg/ml)
TIME AFTER ADMINISTRATION (HOURS)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
0
1
2
3
4
5
6
7
8

FIG. 3

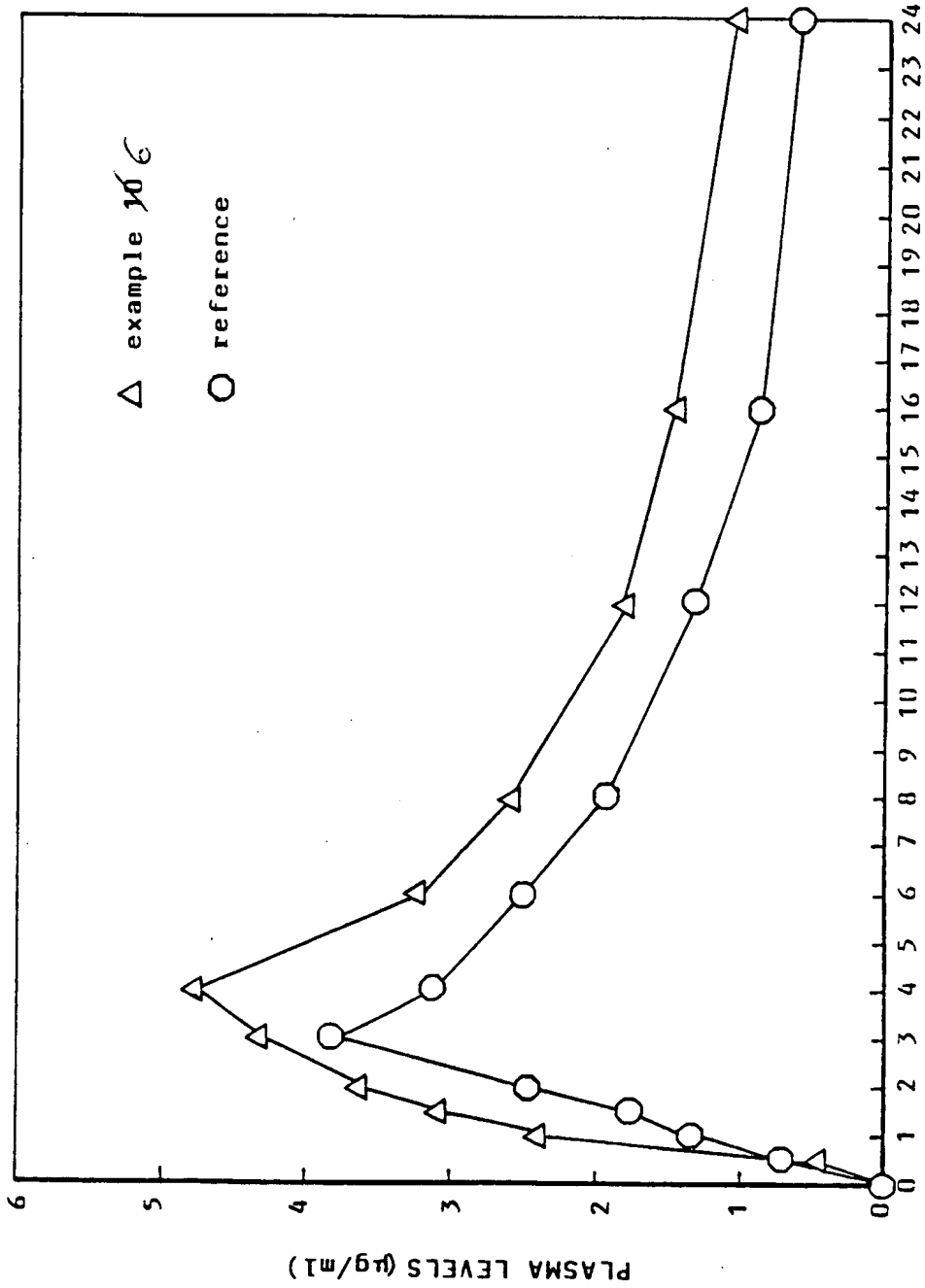
PLASMA LEVELS (µg/ml)
0
1
2
3
4
5
6
TIME AFTER ADMINISTRATION (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
△ example 16
○ reference

FIG 4